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Long-Term Survival Of De Novo Stage Iv Human Epidermal Growth Factor Receptor 2 (her2)-Positive Breast Cancers Treated With Her2 Targeted Therapy

Yao Wong

Long-term Survival of *De Novo* Stage IV Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancers treated with HER2 Targeted Therapy

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Yao S. Wong
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Abstract*

Yao Wong[1], Akshara Singareeka Raghavendra[2], Christos Hatzis[1], Javier Perez Irizarry[1], Teresita Vega,[1] Carlos H. Barcenas[2], Mariana Chavez-MacGregor[2], Vicente Valero[2], Debu Tripathy[2], Lajos Pusztai[1], Rashmi K. Murthy[2]

[1]Yale University School of Medicine
[2]MD Anderson Cancer Center

Background: An increasing number of metastatic HER2 positive cancers are diagnosed as *de novo* stage IV disease. We hypothesize that a subset of these patients, who achieve complete clinical response or no evidence of disease (NED) status after multi-agent HER2-targeted treatments may have long progression free (PFS) and overall survival (OS).

Methods: 483 patients with *de novo* stage IV HER2 positive breast cancer diagnosed between 1998-2015 were identified through the medical records at Yale and MD Anderson Cancer Centers. Treatment, clinical variables and survival were extracted and compared between those who achieved NED status and those who did not.

Results: All patients received trastuzumab and 94 (20%) also received pertuzumab as first line therapy. The median OS was 5.5 years (95% Cl:4.8-6.2). Sixty-three patients (13.0%) achieved NED, their PFS and OS were 100% and 98% (95% CI:94.6%-100%) at 5 years and remined the same at 10 years. For patients with non-NED (n=420), the PFS and OS rates were 12% (95% CI:4.5%-30.4%) and 45% (95% CI:38.4%-52.0%) at 5 years, and 0%, and 4% (95% CI:1.3%-13.2%) at 10 years. There was no difference in age, grade, race, year of diagnosis, ER status, treatment distribution, or radiation between the NED and non-NED groups. NED patients more frequently had solitary metastasis (79% vs 51%, p=0.005) and surgery to resect cancer (59% vs. 22%, p≤0.001). In multivariate analysis, NED status (Hazard ratio (HR):0.014, P=0.0002) and hormone receptor positive status (HR:0.72; P=0.04) were associated with prolonged OS.

Conclusion: Achieving NED status may be an important therapeutic goal for de novo, stage IV, HER-2 positive MBC.

*These results were presented at the 2017 Annual Meeting of the American Society of Clinical Oncology in June 2017 and received a Merit Award.

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Introduction

Metastatic breast cancers (MBC) can be either de novo, stage IV disease or asynchronous metastatic recurrence of stage I-III cancers. An important difference between these two types of metastatic disease is the extent of prior therapies. De novo, stage IV disease implies the presence of distant metastasis at the time of initial diagnosis and no prior therapy for the cancer. Metastatic recurrence of stage I-III breast cancer typically implies recurrence despite systemic adjuvant therapy. Both types of metastatic breast cancers are considered incurable and treated with palliative intent usually with sequential single agent or doublet therapies (1).

In the past 10 years, the inclusion of Human Epidermal Growth Factor Receptor 2 (HER-2) targeted agents into the adjuvant therapy of stage I-III, HER-2 positive breast cancers have significantly reduced distant metastatic recurrences and improved survival (2,3,4). This has resulted in overall fewer HER2 positive MBC and in a relative increase in the proportion of de novo, stage IV disease among patients with HER-2 positive metastatic disease. Historically, de novo, stage IV breast cancer accounted for 6-20% of metastatic breast cancers across subtypes but recent studies reported that over 50% of metastatic HER-2 breast cancers today represent de novo, stage IV disease (5,6,7,8,9). This shift in the proportion of de novo stage IV disease raise an important clinical question. Should de novo stage IV, HER2 positive MBC treated differently from recurrent HER2 positive MBC?

Several studies examined whether clinical outcomes differ between de novo and recurrent MBC. A study that examined the prognostic impact of metastasis-free interval (MFI; i.e. the time between initial diagnosis and distant recurrence) on survival included 154 patients with de novo MBC and showed that these patients had a prolonged survival compared with patients who had a recurrence within 24 months. However, there was no difference in survival compared to patients

who recurred >24 months after diagnosis (10). Results were not presented separately for HER-2 positive patients. Another study, focused on the outcome of HER-2 positive MBC and showed that patients with de novo disease (n=113) receive more aggressive first-line treatments and experienced longer survival compared to those with recurrent disease (n=303). In the de novo cohort, 54 patients who underwent surgery of the primary tumor had significantly longer progression free survival (PFS) (hazard ratio [HR]=0.44; 95% CI:0.26-0.72) and overall survival (OS) (HR=0.49; 95% CI:0.26-0.93) than those who did not have surgery (11). Several other studies that examined clinical features that are associated with long-term survival of HER2 positive MBC treated with HER2 targeted therapies identified hormone receptor positivity, oligometastatic disease, surgical resection of metastases and/or primary tumor and no prior exposure to HER2 targeted therapies (in the adjuvant setting) as predictors of long-term survival (7,8,9,12-15).

The treatment of metastatic HER-2 positive breast cancer has improved substantially over the past 10 years due to the introduction of four distinct HER-2 targeted drugs (trastuzumab, lapatinib, pertuzumab and TDM1)(16,17,18,19). Both randomized clinical trials and population based registries demonstrated substantial improvement in median survival of HER2 positive MBC in the past 15 years (8,9,12-14). As a result, many oncologists can recall anecdotal cases when metastatic, HER-2 positive breast cancer patients treated with HER-2 targeted drugs achieved complete clinical response and had no evidence of disease (NED) for a long time. This raises the possibility that some patients with stage IV, HER-2 positive cancer who receive combined modality HER2-targeted therapies may be cured from their MBC. The patient population where this is the most plausible is newly diagnosed, oligo-metastatic, stage IV disease with no prior HER-2 targeted therapy that achieved no evidence of disease (NED) status with treatment.

Hypothesis

We hypothesize that a subset of patients with *de novo* stage IV HER-2 positive cancers can achieve long progression free survival (PFS) after initial combined modality HER-2 targeted therapies.

Objectives

The primary objective of this study was to assess how often patients with de novo, stage IV HER-2 positive MBC achieve NED with modern HER-2 targeted therapy and what their long-term progression free and overall survival is. The secondary objective was to compare the survival between NED and non-NED patients.

Methods

Patient Population

In order to conduct this research, a chart review protocol was designed titled "A retrospective assessment of long-term survival in *de novo* metastatic HER-2+ breast cancer treated with HER-2 targeted therapy" (PI: Yao Wong, Yale Human Investigations Committee (HIC)# 1607018058). The protocol was approved by the HIC on August 19, 2016. The Smilow Cancer Hospital, Tumor Registry Database and the Connecticut State Tumor Registry was queried for the names and medical record numbers of all HER-2 positive breast cancers diagnosed between September 30, 1998 to December 31, 2015 to identify patients who presented with de novo, stage IV metastatic disease and received trastuzumab containing therapy. In order to maximize the sample size, we have initiated a collaboration with MD Anderson Center (MDACC); Dr Rashmi Murthy served as the MDACC principal investigator for the study. We have provided MDACC with the chart review

protocol and anonymized data without patient identifiers were transferred from MDACC to Yale for final joint data analysis and publication.

Variables of Interest

The following information were extracted from the medical records and stored in an XL data:

Patient demographics: name, date of birth, race

Tumor characteristics: date of diagnosis of metastatic breast cancer, date of diagnosis primary breast cancer if applicable (to distinguish recurrent MBC from de novo stage IV disease and report on frequency of stage IV disease), estrogen and progesterone receptor status, HER-2 status, the number of involved sites with cancer at diagnosis of metastatic cancer (1, 2-5, >5) and the organ site location (categorized as bone, visceral, brain or soft tissue).

Treatment history: If metastatic recurrence occurred after diagnosis of stage I-III cancer, the neoadjuvant or adjuvant chemotherapy (yes vs no, and type of regimen), adjuvant endocrine therapy (yes vs no, and name of agent), first line treatment agents.

The electronic and paper record of each patient was manually reviewed by local study investigators and each site completed an identical data acquisition form.. We also extracted from the charts best response to therapy that was classified either as NED if all imaging evidence of active cancer resolved on imaging or non-NED. Residual sclerotic bone lesions on a computerized tomograph image that has turned metabolically inactive on a PET-CT or resolved on a bone scan were included in the NED category. Survival status was categorized as alive versus deceased and alive with recurrence versus alive without recurrence..

Statistical Analysis

Overall survival was measured from the date of diagnosis of de novo stage IV MBC until the date of death or last follow-up. The PFS was calculated from the start of first-line therapy to the discontinuation of therapy. Survival curves were plotted using the Kaplan-Meier method and factors associated with overall survival and NED status were assessed using multivariate Cox and logistic regression analyses. P-values from Kaplan-Meier and multivariate analysis.

Results

We identified 483 de novo, stage IV, HER2-positive MBC patients who received first line treatment with trastuzumab-based therapy in the two institutions combined. All patients received trastuzumab and 94 patients (20%) also received pertuzumab as first line therapy. The median follow-up for the entire cohort was 2.8 years and OS rates were 54% (n = 483; 95% CI: 48%-60.4%) and 18% (95% Cl: 11.4%-28.3%) at 5 and 10 years, respectively. Sixty-three patients (13%) achieved NED status.

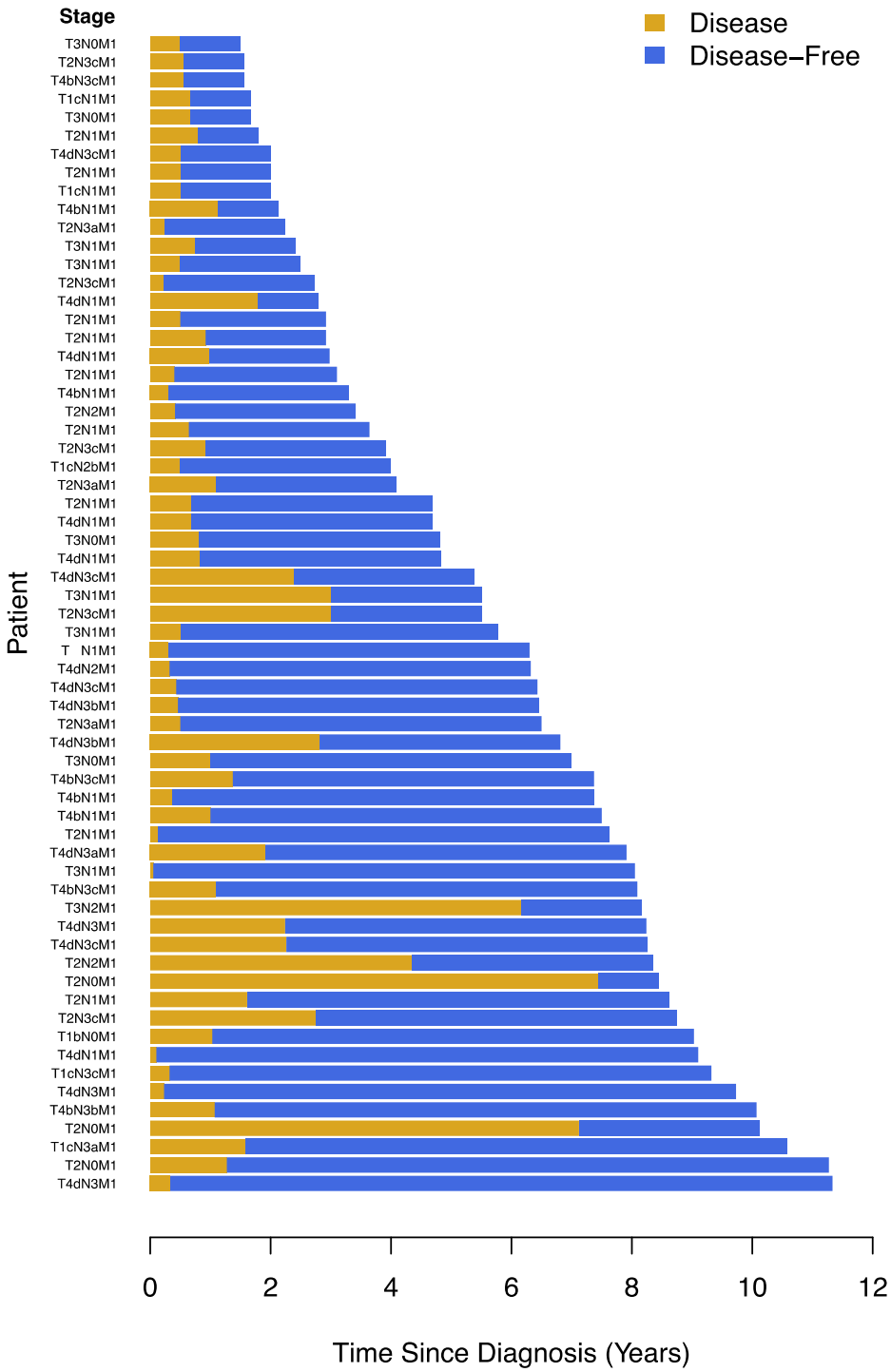
Those who achieved NED had a median age of 49 years, the majority was white (73%), with grade 3 (73%), ER positive (70%) tumors and 79% had single site metastasis. Fifty nine percent of patients with NED underwent surgery of the primary lesion and 57% had radiation therapy. There were no significant differences in age, grade, race, ER status or radiation treatment use between the NED and non-NED cohorts. However, patients in the NED cohort more frequently had single organ site metastasis (79% vs 51%, p = 0.005) and more often had surgery for the primary tumor or a metastatic lesion (59% vs. 22%, p=0.000001). Patient characteristics of the two cohorts are shown on Table 1. Supplementary Table 1 includes tumor characteristics and systemic

treatment for each of the patients who achieved NED. In multivariate analysis, having a single metastatic site, having surgery and oligometastatic bone and CNS involvement were associated with NED status (Table 2).

Table 1. Patient and Tumor Characteristics

	NED Cohort (N=63)	Non NED Cohort (N=420)
Follow up (years) Median (range)	5.5 (1.5-11.3)	2.5 (0.1-10.6)
Age Median (range)	49 (29-70)	50 (25-88)
Race		
White	73%	71%
Black	7%	13%
Hispanic	14%	10%
Other	6%	6%
Grade		
Grade 1	1%	0%
Grade 2	26%	25%
Grade 3	73%	75%
HR+	70%	68%
HR –	30%	32%
Met. Sites		
Visceral	46%	59%
Bone	48%	53%
Soft-tissue/nodes	32%	32%
CNS	0%	7%
# Met. Sites		
1	79%	51%
2	21%	37%
≥3	0%	12%
1st line Therapy		
T	73%	82%
T+P	27%	18%

Figure 2. Disease course of patients who achieved NED status



For the NED cohort, the median survival was not achieved at a median follow-up of 5.5 years. The OS rates were 98% (95% CI:94.6%-100%) at 5 and 10 years. The PFS was 100% at 5 and 10 years indicating no progression for any of the patients who achieved NED (Figure 1 A). Figure 2 shows the follow-up duration and disease status of each NED patient at last follow-up. For patients who did not achieve NED status, the median OS was 4.7 years (95% Cl: 4.2-5.3) at median follow-up of 2.5 years. The OS rates were 45% (95% CI:38.4%-52.0%) and 4% (95% CI:1.3%-13.2%) at 5 and 10 years, respectively. The PFS rates were 12% (95% CI: 4.5%-30.4%) and 0% at 5 and 10 years, respectively (Figure 1 B).

Figure 1. Kaplan-Meier Plots of Overall and Progression-Free Survival by NED status

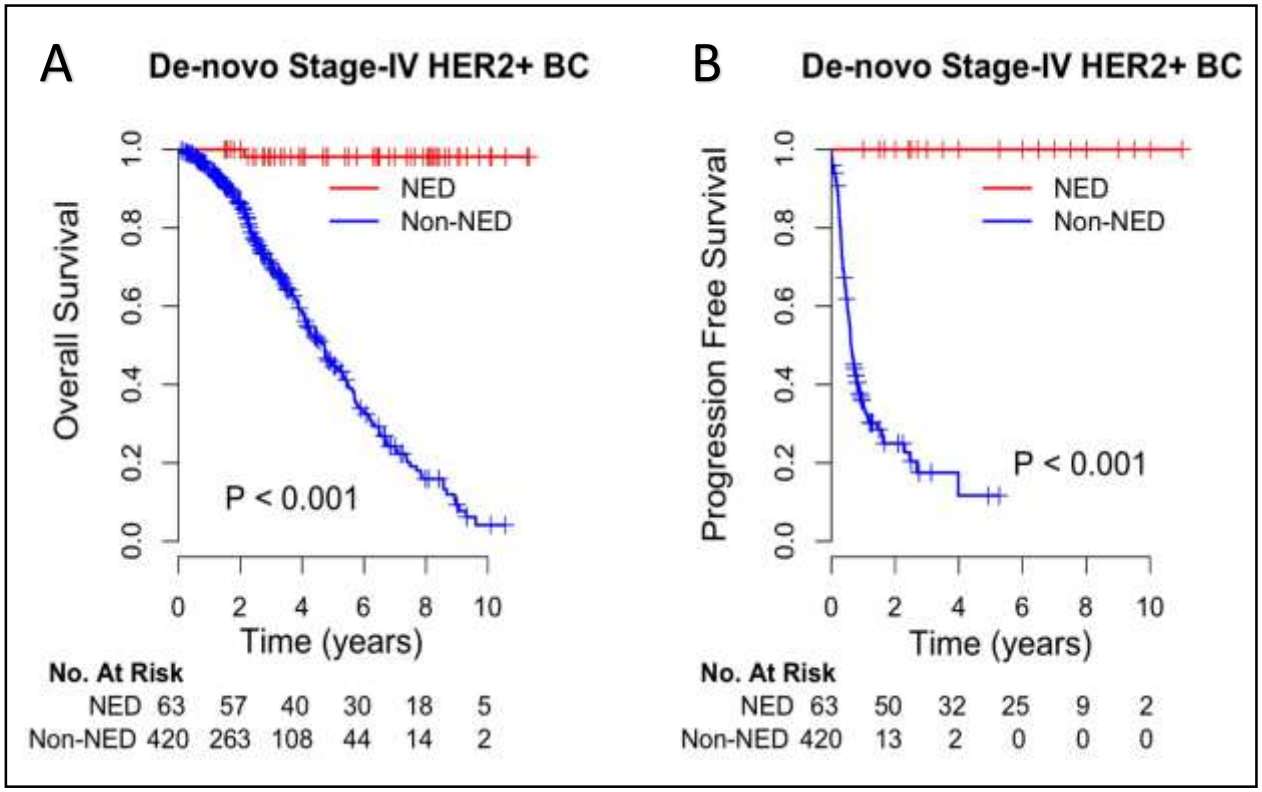


Table 2 gives patient characteristics for NED patients.

Table 2. Stage IV Patients - No Evidence of Disease

PATIENT	AGE	STAGE	ER/PR	METASTATIC SITES	TX
1	32	T4dN3M1	+/+	Bone	THP
2	64	T2N0M1	+/-	Bone	TCH
3	62	T1cN3aM1	+/-	Visceral	TCH
4	56	T4bN3bM1	+/+	Bone	TCH
5	48	T2N0M1	+/-	Visceral	TCH
6	54	T4dN3M1	-/-	Bone, soft tissues	TCH
7	52	T1cN3cM1	-/-	Soft tissues	TH
8	57	T4dN1M1	+/-	Visceral	TH
9	65	T2N0M1	+/-	Bone	Herceptin, arimidex
10	53	T3N2M1	-/-	Visceral	TCH
11	65	T2N1M1	-/+	Visceral, bone	Herceptin, Navelbine
12	60	T2N3cM1	+/+	Visceral, bone	TH
13	39	T1bN0M1	+/+	Visceral	TH
14	39	T4bN3cM1	-/-	Visceral, soft tissue	TH, lapatinib
15	38	T2N2M1	-/-	Visceral	TCH
16	48	T4dN3cM1	-/-	Soft tissues	TCH
17	68	T4dN3M1	+/-	Bone	TH
18	60	T3N1M1	-/-	Visceral, bone	TH
19	43	T2N1M1	-/-	Visceral	TH
20	38	T4dN3aM1	-/-	Bone	Herceptin, abraxane
21	48	T4dN3bM1	+/+	Bone	TH lapatinib,
22	53	T3N0M1	-/-	Visceral	TCH
23	54	T4bN1M1	-/-	Visceral	TH
24	48	T4bN3cM1	-/-	Soft tissues	TH
25	52	T4dN2M1	-/-	Bone	TCH
26	31	T2N3aM1	-/-	Visceral	TH
27	64	T4bN1M1	-/-	Bone	TCH
28	52	T4dN3cM1	-/-	Visceral	TCH
29	47	T N1M1	+/-	Bone	TCH
30	64	T4dN3bM1	+/-	Soft Tissue	TH, lapatinib
31	48	T3N1M1	+/+	Bone, soft tissues	TCH
32	32	T2N3cM1	+/+	Bone	THP
33	62	T3N1M1	+/+	Visceral	THP

34	**44**	**T4dN3cM1**	**+/+**	**Visceral, soft tissues**	**TCH**
35	**53**	**T4dN1M1**	**+/+**	**Bone**	**TH**
36	**44**	**T2N1M1**	**+/+**	**Bone**	**TCH**
37	**49**	**T3N0M1**	**+/+**	**Bone**	**TCH**
38	**49**	**T4dN1M1**	**-/-**	**Soft tissues**	**TH**
39	**30**	**T2N1M1**	**+/+**	**Bone, soft tissues**	**TH**
40	**49**	**T2N2M1**	**-/-**	**Visceral, soft tissues**	**AC-TH**
41	**59**	**T2N1M1**	**+/+**	**Bone**	**THP**
42	**47**	**T4dN1M1**	**+/-**	**Visceral**	**TCH**
43	**51**	**T2N3aM1**	**+/-**	**Bone**	**TCH**
44	**29**	**T2N3cM1**	**-/-**	**Bone, soft tissues, visceral**	**TH**
45	**65**	**T4bN1M1**	**+/-**	**Visceral**	**THP**
46	**29**	**T2N3cM1**	**-/-**	**Soft tissues**	**TCH**
47	**67**	**T2N1M1**	**+/-**	**Visceral, soft tissues**	**TH, lapatinib**
48	**46**	**T3N1M1**	**+/+**	**Soft tissues**	**THP**
49	**39**	**T1cN2bM1**	**+/+**	**Visceral**	**TCH**
50	**57**	**T2N1M1**	**+/-**	**Visceral, soft tissue**	**THP**
51	**70**	**T3N1M1**	**-/-**	**Visceral, soft tissues**	**THP**
52	**32**	**T4dN1M1**	**+/-**	**Visceral tissues**	**THP**
53	**38**	**T4bN1M1**	**+/+**	**Bone**	**THP**
54	**59**	**T1cN1M1**	**+/+**	**Bone**	**TH**
55	**48**	**T2N1M1**	**+/+**	**Bone**	**THP**
56	**35**	**T4dN3cM1**	**-/-**	**Soft tissues**	**TH**
57	**68**	**T2N3aM1**	**-/-**	**Bone**	**TCH**
58	**57**	**T3N0M1**	**-/-**	**Visceral**	**THP**
59	**29**	**T4bN3cM1**	**+/-**	**Bone**	**THP**
60	**51**	**T3N0M1**	**-/-**	**Bone, soft tissues**	**THP**
61	**33**	**T2N1M1**	**+/+**	**Bone, visceral**	**THP**
62	**49**	**T1cN1M1**	**-/-**	**Visceral**	**THP**
63	**61**	**T2N3cM1**	**-/-**	**Soft tissues**	**THP**

THP (docetaxel, trastuzumab, pertuzumab), TCH (docetaxel, carboplatin, trastuzumab), TH (docetaxel, trastuzumab), AC-TH (doxorubicin, cyclophosphamide, docetaxel, trastuzumab), FEC (5-fluorouracil, epidoxorubicin, cyclophosphamide)

In Cox multivariate analysis only achieving NED status (Hazard ratio (HR):0.014, P=0.0002) and hormone receptor positive status (HR:0.72; P=0.04) were associated significantly with prolonged OS (Table 3). For PFS, the Cox model did not converge due to lack of events in the NED group.

Table 3. Factors associated with Overall Survival & NED status in multivariate analysis

Overall Survival	HR	95% CL	P-value
NED vs non-NED status	**0.014**	**0.002, 0.01**	**2.10E-05**
Age	1.01	0.75, 1.35	0.97
Grade (1 or 2 vs 3)	1.13	0.81, 1.58	0.48
Hormone Receptor Status	**0.72**	**0.53, 0.99**	**0.04**
Herceptin Only vs Herceptin + Perjeta	0.96	0.54, 1.72	0.9
Surgery (Y or N)	0.72	0.51, 1.01	0.06
Radiation (Y or N)	1.17	0.86, 1.61	0.32
No. of metastatic sites (1 vs. > or =3)	0.70	0.36, 1.37	0.30
Visceral Involvement (Y or N)	1.34	0.90, 1.98	0.15
Bone Involvement(Y or N)	1.43	0.94, 2.17	0.09
CNS Involvement (Y or N)	1.43	0.79, 2.58	0.23

No Evidence of Disease status	Odds Ratio	95% Confidence Interval	P value
Age (> 50 vs <= 50)	0.953	0.529 to 1.711	0.871
Grade (3 vs 1 or 2)	0.989	0.535 to 1.881	0.973
Hormone Receptor Status (ER+ vs ER-)	0.854	0.471 to 1.556	0.603
Number of metastatic sites (2 vs 1)	**0.207**	**0.075 to 0.520**	**0.001**
Number of metastatic sites (3+ vs 1)	**0.028**	**0.001 to 0.201**	**0.002**
Visceral Involvement (Yes or No)	1.809	0.873 to 3.854	0.116

Bone Involvement (Yes or No)	2.376	1.129 to 5.169	0.025
CNS Involvement (Yes or No)	4.586	1.111 to 16.41	0.023
Trastuzumab only versus trastuzumab + pertuzumab	1.655	0.841 to 3.160	0.134
Surgery (Yes or No)	**4.422**	**2.398 to 8.343**	**<0.001**
Radiation (Yes or No)	0.892	0.481 to 1.556	0.716

Factors significantly associated with achieving NED status were fewer number of metastatic sites, and having surgery of the primary lesion.

Discussion

Several single institution and registry based studies examined long-term survival of MBC and each of these describe a small fraction of patients who experience prolonged survival (9,13,21,22). Due to increasing efficacy of therapies, median survival of patients with MBC has increased in the past decades and a growing minority of patients experience complete clinical response with systemic therapies or achieve an NED status with multi-agent therapy, particularly among HER-2 positive patients (5,6,23). However, the primary goal of treatment remains palliative (1). Several editorials in the past few years hypothesized that cure may be accomplished in MBC (20,24,25). To examine this hypothesis, we assumed that the patients who are most likely to be cured from MBC are those with previously untreated, HER-2 positive cancers because of the highly effective systemic therapies that are available for this population.

In this paper, we examined long-term survival of de novo, stage IV, HER-2 positive breast cancers who did, or did not, achieve NED status with therapy. We found that 13% of patients achieved NED with trastuzumab-based therapy. This is similar to findings by Bishop et al who

assessed 570 HER-2 positive MBC patients and reported that 16% achieved NED with initial therapy (26). In contrast to our study they looked at all metastatic cases, not just the *de novo* subset. In our study, all NED patients were without disease progression at 5 years and their OS was 98% at 10 years. In contrast, for patients who did not achieve NED, the 10-year OS was only 4%. Patients who achieved NED had unique disease characteristics, they typically had single metastasis, often in the bone or CNS, and more frequently underwent surgery to resect the primary tumor or solitary metastasis. These observations are also consistent with earlier reports that identified oligometastatic disease, HER-2 positive status and de novo stage IV presentation as predictors of long-term survival without evidence of disease in MBC.

We suggest that the bulk of the evidence from retrospective studies indicates that achieving NED status in de novo, stage IV, oligometastatic, HER-2 positive breast cancer may be an important therapeutic goal. Dual HER-2 targeted therapies combined with chemotherapy result in high rates (60%-80%) of pathologic complete response rates in early stage disease (27,28) and aggressive multi-agent therapy has reduced distant metastatic recurrence rates and improved survival in locally advanced HER-2 positive breast cancers. Results from retrospective studies raise the possibility that a similar approach might save the life of some woman with oligometastatic, HER-2 positive disease. Applying the neoadjuvant treatment strategy to oligometastatic disease, would imply starting treatment with systemic HER-2 targeted therapy that has the highest probably to induce a complete response, treating until best response, resecting or radiating residual disease, if any, and continuing maintenance therapy with a HER-2 targeted agent and endocrine therapy if appropriate. Since most patients with metastatic disease eventually receive many, if not all, available therapies, including palliative radiation, intensifying treatment

early in the course of the disease in the hope of durable disease control, may not be unreasonable for a select group of patients.

Our study, and all previous retrospective studies, have important limitations. Treatment decisions for individual patients represented in institutional and national data bases are made in the context routine care and are influenced by patient preference, comorbid conditions, physician judgement and evolving practice standards over time. This leads to highly variable therapies for individual patients. Patient selection has clearly influenced our observations that is reflected by the significantly different baseline patient characteristics of the two response cohorts (NED versus non-NED). Therefore, we cannot conclude with certainty that the treatment leading to NED status has caused the excellent long-term survival. We also acknowledge that our follow-up is short and most NED patients have not been followed until 10 years, and late recurrences will occur in our cohort. Nevertheless, we would like to draw attention to the good outcome of a select group of patients who present with previously untreated, HER2 positive metastatic breast cancer and achieve no evidence of disease status with systemic therapy alone or with combined modality treatment Achieving NED status may be important therapeutic goal for this selected group of patients.

References

1. Santa-Maria CA, et al. 2016 Management of Metastatic HER2-Positive Breast Cancer: Where Are We and Where Do We Go From Here? Oncology (Williston Park, N.Y.) 30(2):148-155 ·
2. Perez, E. A., et al. 2014. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. Journal of Clinical Oncology 32(33): 3744-3752.
3. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672, 2005
4. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684, 2005
5. Tripathy, D., et al. 2015. Abstract P3-07-14: Increasing proportion of de novo compared with recurrent HER2-positive metastatic breast cancer: Early results from the systemic therapies for HER2-positive metastatic breast cancer registry study. Cancer Research 75(9 Supplement): P3-07-14-P03-07-14
6. Dzimitrowicz, H., et al. 2016. "T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2–Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab." Journal of Clinical Oncology 34(29): 3511-3517
7. den Brok, WD. et al. "Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed." Breast Cancer Research and Treatment (2016): 1-8.
8. Murthy, RK et. al. 2014. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes HER2-positive metastatic breast cancer outcomes. Cancer. 120(13): 1932-8
9. Vaz-Luis, I et al. "Clinicopathological Features Among Patients With Advanced Human Epidermal Growth Factor–2-Positive Breast Cancer With Prolonged Clinical Benefit to First-Line

Trastuzumab-Based Therapy: A Retrospective Cohort Study." Clinical Breast Cancer 13.4 (2013): 254-263

10. Lobbezoo DJ, Van Kampen RJ, Voogd AC, Dercksen MW, Van Den Berkmortel F, Smilde TJ, Van De Wouw AJ, Peters FP, Van Riel JM, Peters NA, De Boer M. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer?. British journal of cancer. 2015 Apr 28;112(9):1445-51.
11. Lambertini M, Ferreira AR, Di Meglio A, Poggio F, Puglisi F, Sottotetti F, Montemurro F, Poletto E, Bernardo A, Risi E, Dellepiane C. Patterns of Care and Clinical Outcomes of HER2-positive Metastatic Breast Cancer Patients With Newly Diagnosed Stage IV or Recurrent Disease Undergoing First-line Trastuzumab-based Therapy: A Multicenter Retrospective Cohort Study. Clinical Breast Cancer. 2017 Apr 11.
12. Rossi, V et. al. 2014. Clinical outcome in women with HER2-positive *de novo* or recurring stage IV breast cancer receiving trastuzumab-based therapy. Breast. 23(1): 44-9
13. Dawood et. al. 2010. Survival differences among women with *de novo* stage IV and relapsed breast cancer. Ann Oncol. 21(11): 2169-2174.
14. Yardley, DA et. al. 2014. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 145(3): 725-34
15. Harano K, Lei X, Gonzalez-Angulo AM, Murthy RK, Valero V, Mittendorf EA, Ueno NT, Hortobagyi GN, Chavez-MacGregor M. Clinicopathological and surgical factors associated with long-term survival in patients with HER2-positive metastatic breast cancer. Breast cancer research and treatment. 2016 Sep 1;159(2):367-74.

16. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001
17. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-2743, 2006
18. Baselga J, Cortes J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-119, 2012
19. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-1791, 2012
20. Hayes DF. Is Breast Cancer a Curable Disease? *J Clin Oncol* 2016;12(1):13-16.
21. Greenberg, P.A.C., et al. 1996. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. Journal of Clinical Oncology. 14(8): 2197-2205
22. Cheng YC, Ueno NT. Improvement of survival and prospect of cure in patients with metastatic breast cancer. *Breast cancer.* 2012;19(3):191-199.
23. Mariotto, Angela B., et al. "Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States." Cancer Epidemiology and Prevention Biomarkers (2017) Published Online, May 18, 2017
24. Sledge GW, Jr. Curing Metastatic Breast Cancer. *J Clin Oncol.* 2016;12(1):6-10
25. Davidson NE. Conquering Metastatic Breast Cancer. *J Onc Practice.* 2016;12(1):11-12.
26. Bishop, AJ et. al. 2015. Prognosis for patients with metastatic breast cancer who achieve a no-evidence-of-disease status after systemic or local therapy. Cancer. 121(24): 4324-32

27. Buzdar AU, Suman VJ, Meric-Bernstam F, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. The Lancet Oncology. 2013;14(13):1317-1325.
28. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of oncology. 2013;24(9):2278-2284.